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Immediate breast reconstruction is oncologically safe for node-positive patients

Comparison using propensity score matching

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Abstract

The oncological safety of immediate breast reconstruction (IBR) in lymph node-positive patients is unclear. In the present study, the impact of IBR on recurrence based on data of patients with axillary lymph node metastases only was examined.

The subjects were 232 patients who underwent breast surgery. The patients were grouped into 2 cohorts: non-IBR patients who underwent mastectomy with axillary lymph node dissection; and IBR patients with tissue expander or flap transfer and axillary lymph node dissection. The Non-IBR group included 165 patients, and the IBR group included 67 patients. For the comparison of oncological outcomes between the 2 groups, propensity score matching was performed. The propensity scores were calculated by logistic regression analysis, including age, tumor staging, human epidermal growth factor receptor 2 status, and estrogen receptor status. There was no difference in locoregional recurrence-free survival (LRRFS) between the non-IBR and IBR groups. The 5-year LRRFS rate was 78.9% in the non-IBR group and 85.1% in the IBR group. There was no difference in recurrence-free survival (RFS) between the non-IBR and IBR groups. The 5-year RFS rate was 75.6% in the non-IBR group and 78.8% in the IBR group. In all patients, the 5-year LRRFS rate was 77.3%, and the RFS rate was 70.5%. Multivariate Cox regression analysis to identify factors affecting RFS in all patients showed that estrogen receptor status and high nuclear grade were significant prognostic factors; IBR was irrelevant.

This is the first report of an analysis using propensity score matching limited to node-positive breast cancer patients, and it showed that IBR is relatively safe in such patients.

Abbreviations: ALND = axillary lymph node dissection, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, IBR = immediate breast reconstruction, IHC = immunohistochemistry, LRRFS = locoregional recurrence-free survival, NG = nuclear grade, NSM = nipple-sparing mastectomy, PMRT = postmastectomy radiation therapy, PSM = propensity score matching, RAM flap = rectus abdominis muscle flap, RFS = recurrence-free survival, SSM = skin-sparing mastectomy, TE = tissue expander.

Keywords: breast cancer, immediate breast reconstruction, locoregional relapse-free survival, node-positive, propensity score matching, relapse-free survival

1. Introduction

The number of patients requesting breast reconstruction after breast cancer mastectomy is increasing every year. Breast reconstruction can be divided into 2 types depending on the timing of the reconstruction: immediate breast reconstruction (IBR) and delayed breast reconstruction. It is well established that IBR provides psychological benefits and improves quality of life.[1] Patients often request IBR. On the other hand, surgeons wonder if IBR should be performed aggressively when there are several concerns. For example, in cases where radiation therapy is

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expected to be used or in reconstructive procedures for patients after radiation therapy, complications are expected to increase.[2–4] The oncological safety and risk of complications must be considered. For example, recurrence may be difficult to detect after IBR.[5] It has been reported that local recurrence after reconstruction with autologous tissue is more difficult to resect than after reconstruction with implants.[6] Another issue is that IBR, especially autologous reconstruction, may affect the oncological treatment because potential complications associated with more extensive surgery may delay adjuvant treatment.[7,8]

Meanwhile, there are a growing number of reports that IBR can be performed safely.[9–13] The recurrence rate is low, especially for early-stage breast cancer, and there are no oncological problems with IBR. The current focus is more on the appropriateness of IBR for advanced breast cancer, which has a relatively high incidence of local and distant recurrence. In particular, the appropriateness of IBR in patients with lymph node metastases is an important clinical question. Patients with positive axillary lymph nodes have more local and distant recurrences than those with negative nodes. Axillary lymph node dissection (ALND) with lymph node metastasis is a routine adjunct to mastectomy for the staging and management of women with breast cancer.[14] ALND is a risk factor for developing complications in IBR patients.[15,16] Complications can lead to delays in adjuvant therapy and oncological problems. In other words, we need to examine whether IBR is oncologically safe for patients with axillary lymph node metastasis compared with no reconstruction, and to the best of our knowledge, there have been no reports dealing only with patients with axillary lymph node metastases. In the case of breast cancer, recurrence often occurs after some time interval. With the increasing number of patients at our institution being followed long-term after primary reconstruction, we thought that we could examine the impact of IBR on recurrence. Thus, the aim of the present study was to investigate the impact of IBR on recurrence based on data from patients with axillary lymph node metastases.

Since IBR is performed at the patient's request, it is not possible to randomize IBR and non-IBR patients. This inevitably results in a retrospective analysis, which has the added problem of differences in patient background characteristics. To resolve this problem, the data were analyzed using propensity score matching (PSM). Although there have been many studies using PSM, this is the first report to examine breast IBR in patients with positive axillary lymph nodes using PSM.

2. Materials and methods

2.1. Patients

All patients who underwent breast surgery at TMDU Medical Hospital between January 2003 and November 2017 were identified. Patients who underwent breast reconstruction after mastectomy and axillary dissection were reviewed. Sentinel lymph node biopsy was performed if axillary node metastases were not evident preoperatively, and additional axillary dissection was performed if metastases were larger than micrometastases. The exclusion criteria for the present study were as follows: patients with distant metastasis; patients who could not provide consent; patients who had not received standard adjuvant treatment; and patients without follow-up records. The studies involving human participants were reviewed and approved by the Institutional Review Board of the TMDU Medical Hospital. The patients/participants provided written, informed consent to participate in the study.

2.2. Comparison of clinical outcomes using propensity score matching

The patients were grouped into 2 cohorts: non-IBR patients who underwent mastectomy and ALND, and IBR patients treated with tissue expander (TE) or flap transfer after mastectomy and ALND. To compare oncological outcomes between the 2 groups, propensity score matching was performed. The propensity scores were calculated by logistic regression analysis, including age and American Joint Committee on Cancer status 7th ed. tumor staging,[17] estrogen receptor (ER) status, and human epidermal growth factor receptor 2 (HER2) status. Patients were matched by propensity score using the nearest-neighbor method with a matching ratio of 1:1. The caliper width was equal to $0.2 \times$ the standard deviation of the logit of the propensity score. After matching, the covariate balance was reviewed for statistical significance and standardized differences.

2.2.1. Immunohistochemistry. All specimens were analyzed by pathologists from our institution, TMDU Medical Hospital, and specimens were considered ER-positive or progesterone receptor-positive on immunohistochemistry (IHC) with staining rates $>10\%$. For HER2 receptor values, IHC 3+ was defined as breast cancer with strong, complete membrane staining observed in at least 10% of tumor cells. For HER2 receptor overexpression of 2 +, gene amplification with fluorescence in situ hybridization was performed.

2.2.2. Operative technique. Reconstruction is mainly indicated in patients with T1/T2 disease. Nipple-sparing mastectomy (NSM) and skin-sparing mastectomy (SSM) were performed in T1 patients. Total mastectomy with skin removal was indicated in T2 patients, or if there was a possibility that the tumor was close to the skin. Even if the tumor was small, if multiple axillary lymph node metastases were suspected, a total mastectomy with skin removal was performed. NSM was not indicated if the lesion was within 2 cm of the nipple. Breast reconstruction was not recommended for patients expected to receive radiation, for example, T3 or suspected multiple lymph node metastasis. However, the surgery was performed according to each patient's wishes, with the patient's understanding and informed consent, after explaining that it was not indicated. The IBR method was as follows: TE, latissimus dorsi myocutaneous flap, deep inferior epigastric artery perforator flap , or rectus abdominis muscle flap (RAM flap). A plastic surgeon was consulted, and the decision was made based on the patient's body shape, breast volume, history, and wishes.

2.2.3. Statistical analysis. Statistical analyses of 2×2 contingency tables of categorical variables were performed using Fisher exact test. The mean duration of survival was calculated using the Kaplan–Meier method. Comparisons between groups were performed using the log-rank test. Logistic regression and Cox regression models were used to analyze the effects of continuous numeric variables on clinical outcomes. Locoregional relapse-free survival (LRRFS) was defined as the time between breast cancer surgery and the detection of locoregional recurrence by biopsy or imaging. Locoregional recurrence was defined as pathologically confirmed disease recurrence in the ipsilateral chest wall or within the supraclavicular, subclavian, ipsilateral axillary, or ipsilateral

internal mammary lymph nodes. Relapse-free survival (RFS) was calculated as the time between surgery and the first relapse. All statistical tests were 2-sided, with $P < .05$, as the threshold for significance. All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html), which is a graphical user interface for R (The R Foundation for Statistical Computing). EZR is a modified version of R Commander designed to add statistical functions frequently used in biostatistics.[18]

3. Results

3.1. Baseline characteristics and propensity score matching

Between January 2003 and December 2017, 1754 patients underwent surgery at the TMDU Medical Hospital for primary breast cancer. A total of 232 patients met the study criteria. The baseline characteristics of the patients are summarized in Table 1. There were 165 IBR and 167 non-IBR patients. There were significant differences in age, ER status, and whether postmastectomy radiation therapy (PMRT) was performed. The resection method was mastectomy in all cases of non-IBR, but SSM, NSM, and mastectomy were performed in IBR cases. They underwent propensity score matching based on age, cancer American Joint Committee on Cancer tumor stage, HER2 status, and ER status, which resulted in the inclusion of 86 patients (43 non-IBR and 43 IBR) for further analysis (Fig. 1). ER and age as background characteristics that differed between the 2 groups and other factors such as stage and HER2 status, which have an important impact on relapse, were matched.

The patients' characteristics in the 2 groups before and after propensity score matching (PSM) are shown in Table 2. After PSM, there were no differences between the 2 groups in age, cancer stage, with or without chemotherapy, nuclear grade (NG), with or without PMRT, ER status, and HER2 status. Of the 43 IBR patients, the breakdown of reconstruction was as follows: TE (n = 22, 51.2%), latissimus dorsi myocutaneous flap (n = 6, 14.0%), deep inferior epigastric artery perforator flap (n = 10, 23.3%), and RAM flap (n = 5, 11.6%). The following were the mastectomy procedures performed in the IBR group: SSM (n = 19, 44.2%), NSM (n = 15, 34.9%), and total mastectomy (n = 9, 20.9%).

3.2. LRRFS and disease-free survival in the non-IBR group and IBR group after PSM

There was no difference in LRRFS between the non-IBR and IBR groups. During follow-up, locoregional recurrence occurred in 6 patients in the non-IBR group and 5 patients in the IBR group. The 5-year LRRFS rate was 78.9% in the non-IBR group and 85.1% in the IBR group. The 8-year LRRFS rates were 69.8% and 81.7% in the non-IBR and IBR groups, respectively ($P = .378$) (Fig. 2). There was no difference in RFS between the non-IBR and IBR groups. During follow-up, distant recurrence was found in 10 patients in the non-IBR group and 11 patients in the IBR group. The 5-year RFS rates were 75.6% and 78.8% in the non-IBR and IBR groups, respectively. The 8-year RFS rates were 65.7% and 72.3% in the non-IBR and IBR groups, respectively ($P = .805$) (Fig. 3).

Table 1

Background characteristics of all surgical cases.

Factor	Non-IBR	IBR	*P* value
n	165	67	
Age (years old)	60.11 ± 12.44	45.82 ± 7.69	<.001
Stage (%)			
IIA, IIB	86 (52.1)	46 (68.7)	
IIIA, IIIB, IIIC	79 (47.9)	21 (31.3)	.28
ER (%)			
Positive	120 (73.6)	60 (90.9)	
Negative	43 (26.4)	6 (9.1)	.004
HER2 (%)			
Positive	21 (13.2)	8 (12.1)	
Negative	138 (86.8)	58 (87.9)	1.000
Nuclear grade (%)			
3	55 (34.1)	20 (29.9)	
1, 2	106 (65.8)	47 (70.1)	.643
PMRT (%)			
Yes	62 (37.6)	13 (19.4)	
No	103 (62.4)	54 (80.6)	.008
Chemotherapy (%)			
Yes	121 (73.3)	53 (79.1)	
No	44 (26.7)	14 (20.9)	.406
Locoregional recurrence (%)			
Yes	22 (13.3)	6 (9.0)	
No	142 (86.1)	61 (91.0)	.563
Distant recurrence (%)			
Yes	45 (27.3)	17 (25.4)	
No	119 (72.1)	50 (74.6)	.908
Mastectomy type			
Bt	165	13	
SSM	0	32	
NSM	0	22	
Reconstruction type			
TE	0	38	
LD flap	0	10	
DIEP	0	13	
RAM	0	6	

Bt = breast mastectomy, DIEP flap = deep inferior epigastric artery perforator flap, IBR = immediate breast reconstruction, LD flap = latissimus dorsi myocutaneous flap, NSM = nipple-sparing mastectomy, PMRT = postmastectomy radiation therapy, RAM flap = rectus abdominis muscle flap, SSM = skin-sparing mastectomy, TE = tissue expander.

3.3. LRRFS and RFS in all patients and predictors of RFS in all patients

The LRRFS and RFS curves are shown in Figs. 4 and 5, respectively. The 5-year LRRFS and RFS rates were 77.3% and 70.5%, respectively. The 8-year LRRFS and RFS rates were 69.0% and 61.2%, respectively. The results of the univariate Cox regression analysis conducted to identify the factors affecting RFS in all patients are shown in Table 3. The risk ratios for ER status, stage, high NG, PMRT, and non-IBR were significant. Multivariate Cox regression analysis conducted to identify factors related to RFS in all patients showed that ER status and high NG were significant prognostic factors, whereas IBR was irrelevant.

4. Discussion

IBR is widely and commonly performed. IBR for early stage breast cancer is a very useful procedure, and its safety and contribution to quality of life have been well documented in various reports.[1] However, whether IBR for advanced cancer is

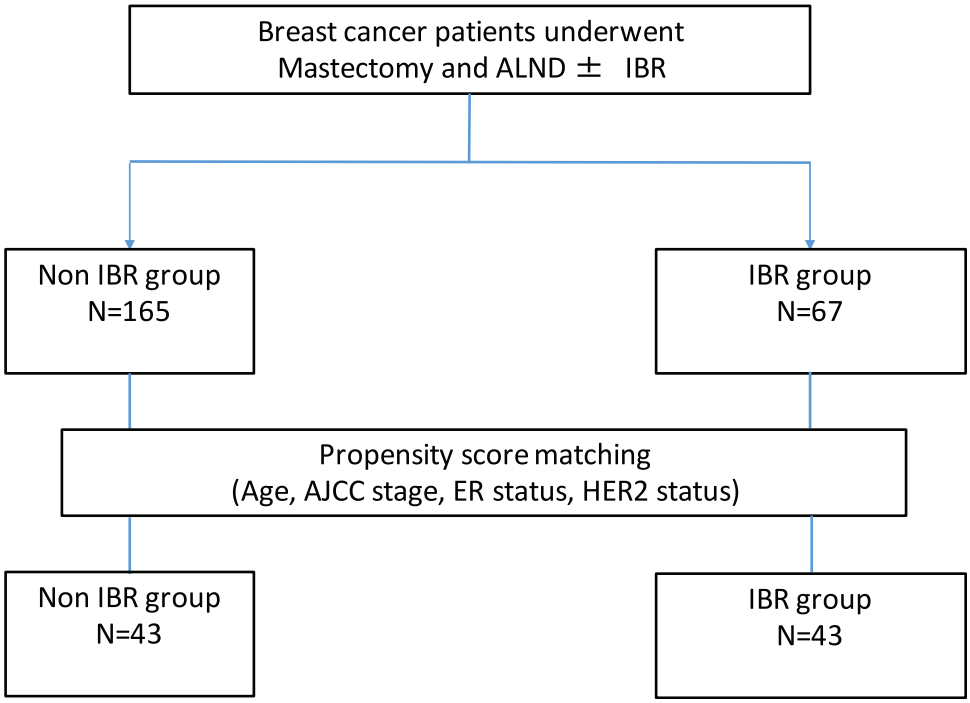

Figure 1. Patient diagram. Propensity score matching based on age, cancer AJCC tumor staging, HER2 status, and ER status was performed. The non-IBR and IBR groups each have 43 matched patients who were included in the primary analysis. AJCC = American Joint Committee on Cancer, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, IBR = immediate breast reconstruction.

Table 2

Patients' background characteristics after propensity score matching.

Factor	Non-IBR	IBR	*P* value
n	43	43	
Age (years old)	48.00 ± 7.90	48.30 ± 6.74	.967
Stage (%)			
IIA, IIB	22 (51.2)	25 (58.1)	.517
IIIA, IIIB, IIIC	21 (48.8)	18 (41.9)	
ER (%)			
Positive	39 (90.7)	38 (88.4)	1.000
Negative	4 (9.3)	5 (11.6)	
HER2 (%)			
Positive	7 (16.3)	5 (11.6)	.757
Negative	36 (83.7)	38 (88.4)	
Nuclear grade (%)			
3	13 (30.2)	12 (27.9)	1.0000
1,2	30 (69.8)	31 (72.1)	
PMRT (%)			
Yes	16 (37.2)	10 (23.3)	.240
No	27 (62.8)	33 (76.7)	
Chemotherapy (%)			
Yes	40 (93.0)	36 (83.7)	.313
No	3 (7.0)	7 (16.3)	
Locoregional recurrence (%)			
Yes	6 (14.0)	5 (11.6)	1.000
No	37 (86.0)	38 (88.4)	
Distant recurrence (%)			
Yes	10 (23.3)	11 (25.6)	1.000
No	33 (76.7)	32 (74.4)	

IBR = immediate breast reconstruction, PMRT = post mastectomy radiation therapy.

safe from an oncological point of view remains unclear, since it is associated with concerns about delays in postoperative anticancer therapy[19] and incomplete radiation therapy. First, there are concerns that such incomplete treatment could lead to an increase in recurrence. Second, there is concern that the physical presence of an implant or autologous tissue would mask detection of a locoregional recurrence.[7,20] Axillary node-positive breast cancer, similar to other cancers, has a high risk of postoperative recurrence.[21] In addition, axillary lymph node dissection is a risk factor for complications in immediate reconstruction.[14–16] Complications may lead to delays in adjuvant therapy.[22] Therefore, IBR patients, especially those with node-positive disease who have a higher recurrence rate, should be reviewed after long-term follow-up to determine whether it is an oncologically safe procedure. Therefore, we decided to investigate the oncological safety of IBR in advanced cancers, especially in node-positive breast cancer.

Several studies have examined the oncological safety of total mastectomy versus total mastectomy with reconstruction.[12,23–25] The number of reports on the safety of immediate reconstruction for advanced breast cancer is gradually increasing. Wang et al[26] demonstrated the oncological safety of immediate reconstruction for T4 breast cancer using data from the Surveillance, Epidemiology, and End Results (SEER) database. Dudley et al[27] showed that women with stage II/III breast cancer selected for IBR had similar rates of ipsilateral local-regional recurrence compared with those undergoing mastectomy alone. However, because IBR itself is performed at the patient's request, randomized trials are difficult to perform. We decided to compare the results using PSM to reduce bias in the patient background characteristics. In addition, we decided to focus on advanced breast cancer. To the best of our knowledge, no studies have used

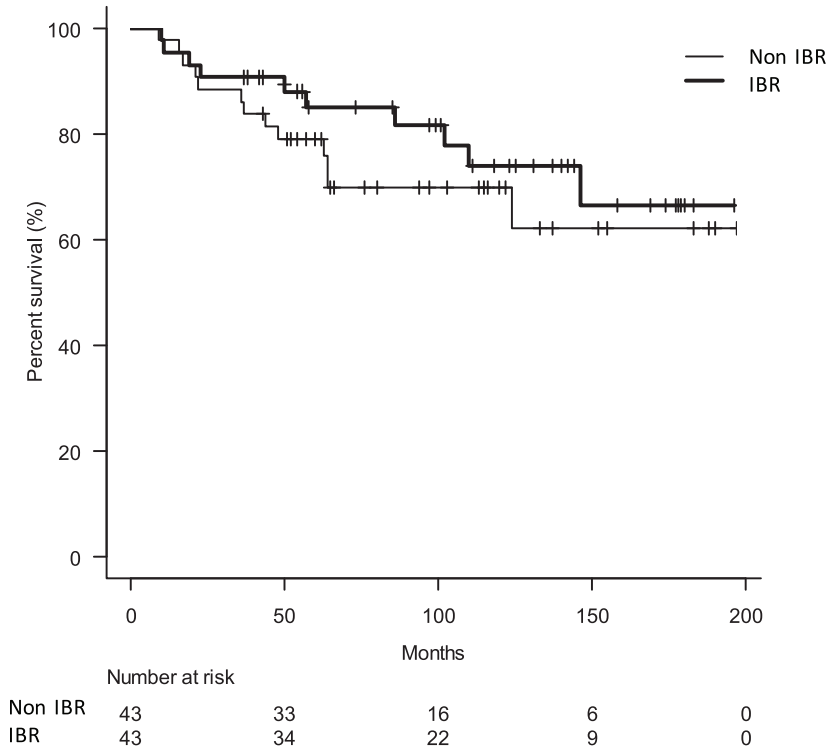

Figure 2. Locoregional relapse-free survival (LRRFS) in propensity score-matched patients. The 5-year LRRFS rate is 78.9% in the non-IBR group and 85.1% in the IBR group. The 8-year LRRFS rate is 66.5% in the non-IBR group and 81.7% in the IBR group ($P = .252$). IBR = immediate breast reconstruction.

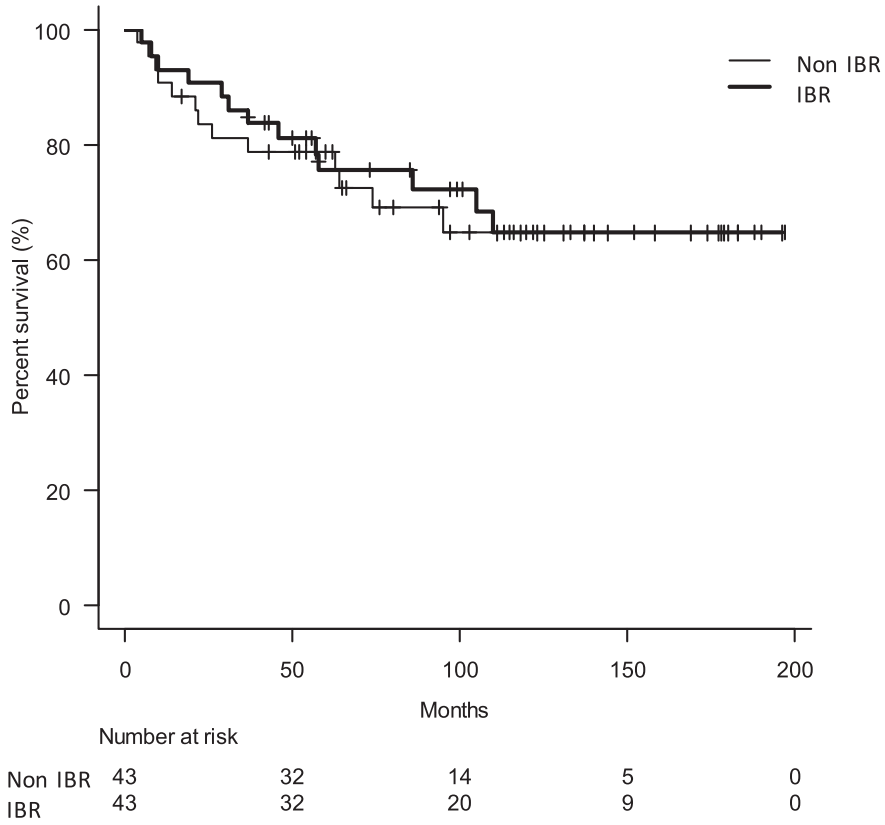

Figure 3. Relapse-free survival (RFS) in propensity score-matched patients. The 5-year RFS rate is 76.4% in the non-IBR group and 75.6% in the IBR group. The 8-year RFS rate is 65.7% in the non-IBR group and 72.3% in the IBR group ($P = .784$). IBR = immediate breast reconstruction.

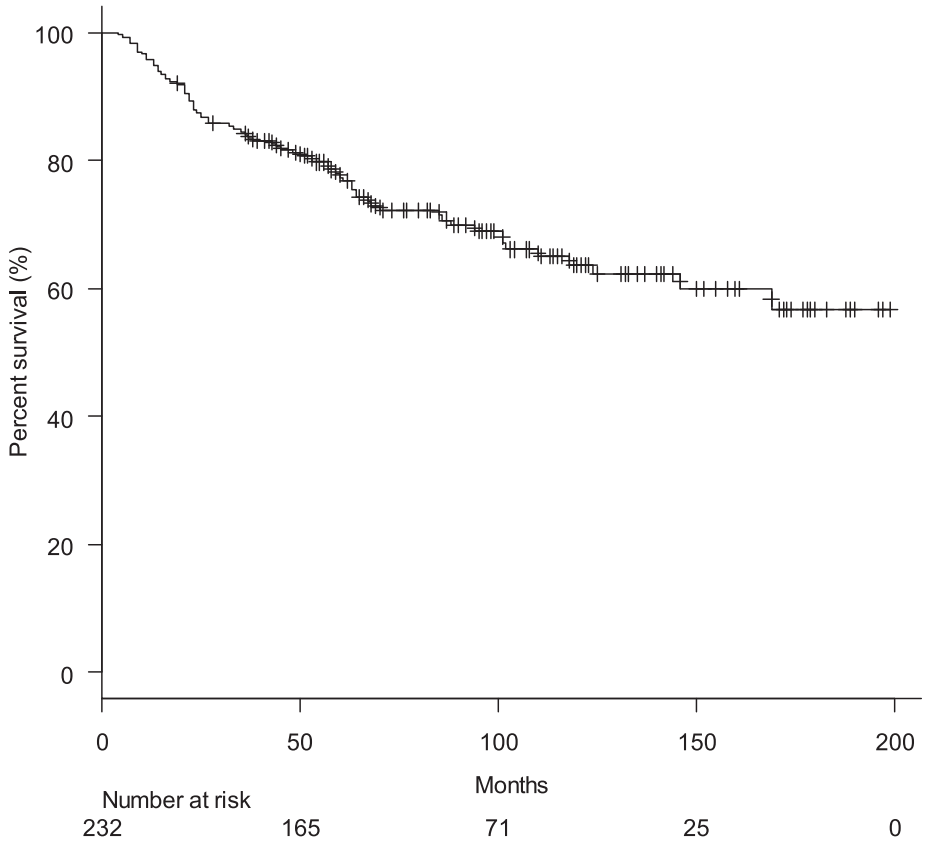

Figure 4. LRRFS in all patients. Loco-regional relapse-free survival (LRRFS) in all patients. The 5-year LRRFS rate is 77.3%, and the 8-year LRRFS rate is 69.0%.

propensity score matching to compare locoregional and distant metastasis rates between non-IBR and IBR only in advanced breast cancer patients. In the present study, IBR was shown to be relatively safe for lymph node-positive breast cancer. This is consistent with the results of this previous study. Furthermore, the analysis using PSM minimized the bias in background factors, which is a problem when considering reconstructive surgery.

Our surgical technique and indications may have some effects on local recurrence. For example, for lesions larger than 2 cm or just below the skin, even if there is no skin invasion, total mastectomy is chosen, not NSM or SSM. NSM is also not indicated for lesions that are close to the nipple. A nipple-tumor distance >2 cm was necessary. The distance from the nipple to the tumor was reported to be 1 to 2 cm in many reports from other centers,[28,29] and our indication may be slightly too strict. On the other hand, there is a report that distance did not correlate,[30] so it is unclear how much this indication affects the results. In any case, the spread and progression of the lesion on preoperative contrast-enhanced MRI should be assessed by a skilled radiologist, and this may also help determine the indication.

Subtype, stage, NG, HER2 status, and Ki67 have been reported as risk factors for distant recurrence.[31,32] In fact, in the present study, ER and NG were identified as factors related to RFS. Ha et al[33] used PSM as in the present study to compare the oncological aspects of flap reconstruction and prosthesis reconstruction and concluded that flap surgery had slightly worse results. Surgical stress-induced perioperative immunomodulation may be prominently involved in anti-metastatic immune activity.[34,35] Because flap reconstruction requires a longer operative time than implant reconstruction, surgical stress may be greater and affect oncological outcomes. In the present study, the percentage of prosthetic breast reconstruction was 50%, but the results may change if the percentage differs.

This study had several limitations. This retrospective study was conducted without randomization and included a small patient sample from a single institution. The number of events was relatively small. The use of PSM, in addition to including only node-positive patients, resulted in a decrease in the number of cases and events. More cases are needed to improve the accuracy of the results. Because of the small number of cases in this study, autologous and prosthetic reconstructions were not examined separately. Whether this has an impact on recurrence should be examined in future studies.

5. Conclusion

This is the first report of an analysis using PSM limited to node-positive patients. The results showed that IBR was oncologically safe in node-positive breast cancer patients. It is important to note that, although this was a PSM analysis, it was not a completely randomized analysis. A more detailed study will require more cases and long-term follow-up.

Author contributions

Goshi Oda performed the surgery, wrote the manuscript, analyzed the data, and performed the statistical analysis. Tsuyoshi Nakagawa, Noriko Uemura, and Hiroki Mori

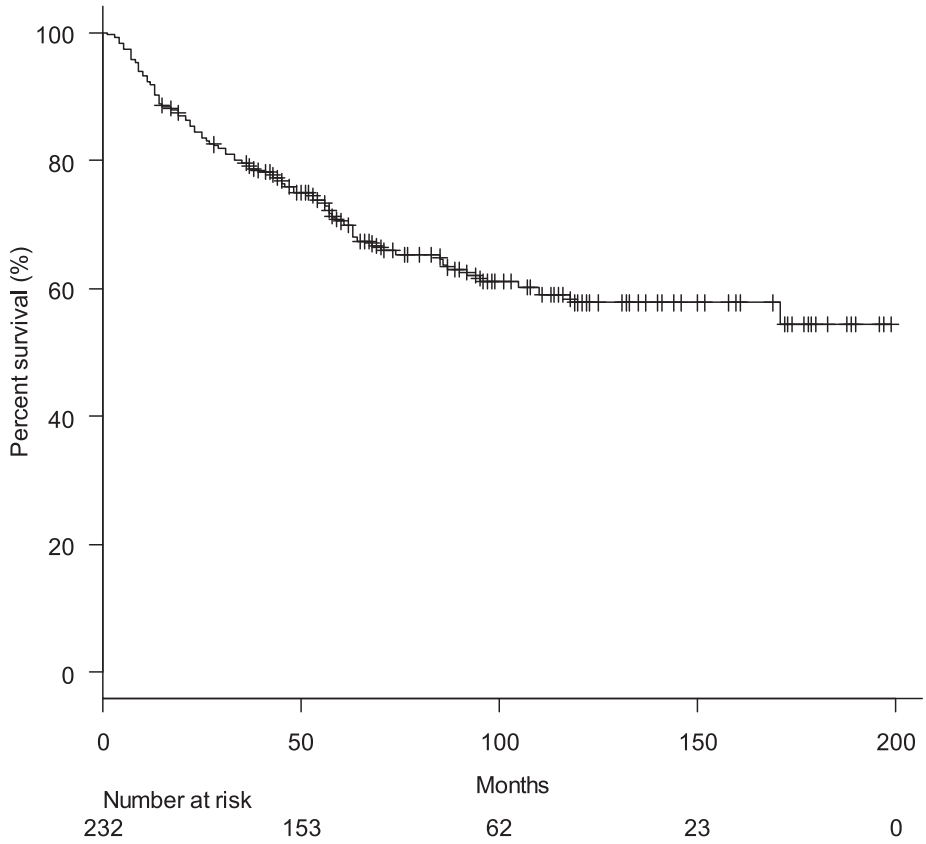

Figure 5. RFS in all patients. Relapse-free survival (RFS) in all patients. The 5-year RFS rate is 70.5%, and the 8-year RFS rate is 61.2%.

Table 3

Univariate and multivariate Cox regression analyses for relapse-free survival in all patients.

	Risk ratio	95% CI	*P*-value	Risk ratio	95% CI	*P*-value
ER Positive vs negative	0.329	0.2054–0.5235	.00000299	0.3942	0.2410–0.645	.000211
HER2 Positive vs negative	1.44	0.794–2.612	.23			
Stage High vs low	2.177	1.404–3.376	.0005061	1.707	0.904–2.281	.07599
Nuclear grade High vs low	1.997	1.287–3.099	.002044	1.6890	1.0770–2.649	.0225
Chemotherapy Yes vs no	1.331	0.769–2.303	.3071			
PMRT Yes vs no	0.4996	0.3213–0.7769	.002067	0.7621	0.4191–1.386	.3732
Age >40 vs ≤40	10.23	0.6552–1.597	.921			
IBR vs non IBR	0.5897	0.3519–0.9881	.04493	0.7503	0.4384–1.284	.2948

IBR = immediate breast reconstruction, PMRT = post mastectomy radiation therapy.

performed the surgery and collected the data. Mio Mori and Tomoyuki Fujioka are responsible for diagnostic imaging and ultrasonography-guided biopsy. Iichiroh Onishi was responsible for pathological evaluations. Hiroyuki Uetake designed the study and wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Data curation: Noriko Uemura, Hiroki Mori, Mio Mori, Tomoyuki Fujioka, Iichiroh Onishi.
Writing – original draft: Goshi Oda.
Writing – review & editing: Tsuyoshi Nakagawa.

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